Amenorrhea

DEFINITION:

Amenorrhea means absence of menstruation.

It is a symptom and not a disease.

Classification of the amenorrhea

1. **PRIMARY AMENORRHEA**
2. **Secondary amenorrhea**

1. Primary amenorrhea is the absence of menstruation by 16 years of age in the presence of normal secondary sexual characteristics, or by 14 years of age if secondary sexual characteristics have not developed.

2. Secondary amenorrhea periods have not occurred for 6 months.

There are at least five basic factors involved in the onset and continuation of normal menstruation.

These are:

* Normal female chromosomal pattern (46XX).

* Coordinated hypothalamo pituitary ovarian axis.

* Anatomical presence and patency of the outflow

tract.

* Responsive endometrium.

* Active support of thyroid and adrenal glands

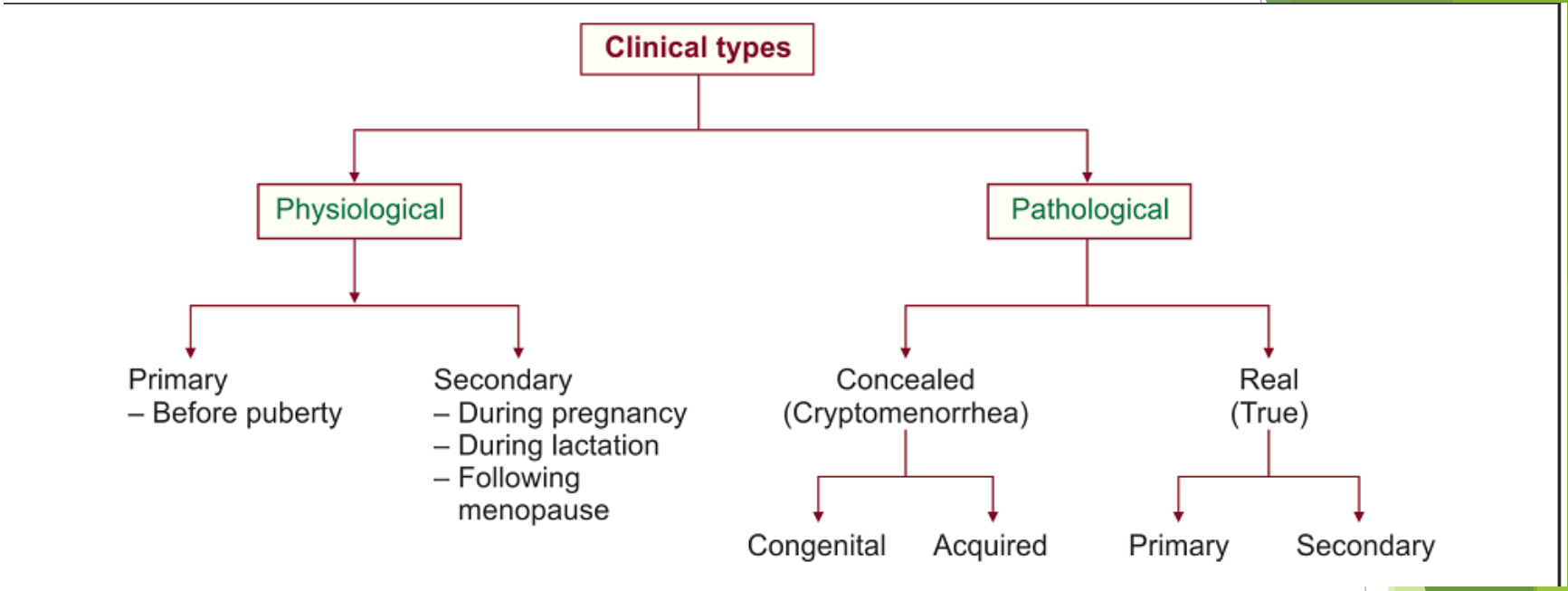
Table 16-1 Primary Amenorrhea: Frequency of Etiologies

Presentation	Frequency (%)
Hypergonadotropic hypogonadism	43
45,X and variants	27
46,XX	14
46,XY	2
Eugonadism	30
Müllerian agenesis	15
Vaginal septum	3
Imperforate hymen	1
AIS	1
PCOS	7
CAH	1
Cushing and thyroid disease	2
Low FSH without breast development	27
Constitutional delay	14
GnRH deficiency	5
Other CNS disease	1
Pituitary disease	5
Eating disorders, stress	2

AIS = androgen insensitivity syndrome; CAH = congenital adrenal hyperplasia; CNS = central nervous system; FSH = follicle-stimulating hormone; GnRH = gonadotropin-releasing hormone; PCOS = polycystic ovarian syndrome.

Adapted from Reindollar, 1981, with permission.

Etiology	Frequency (%)
Low or normal FSH level: various	67.5
Eating disorders, stress	15.5
Nonspecific hypothalamic	18
Chronic anovulation (PCOS)	28
Hypothyroidism	1.5
Cushing syndrome	1
Pituitary tumor/empty sella	2
Sheehan syndrome	1.5
High FSH level: gonadal failure	10.5
46,XX	10
Abnormal karyotype	0.5
High prolactin level	13
Anatomic	7
Asherman syndrome	7
Hyperandrogenic states	2
Late-onset CAH	0.5
Ovarian tumor	1
Undiagnosed	0.5


Clinical types
Physiological
Pathological
Primary
– Before puberty
Secondary
– During pregnancy
– During lactation
– Following menopause
Concealed (Cryptomenorrhea)
Real (True)
Congenital
Acquired
Primary
Secondary

PHYSIOLOGICAL

Before Puberty:

The pituitary gonadotropins are not adequate enough

to stimulate the ovarian follicles for effective

steroidogenesis → estrogen levels are not sufficient

enough to cause bleeding from the endometrium.

During Pregnancy

Large amount of estrogens and chorionic gonadotropins secreted from trophoblasts suppress

the pituitary gonadotropins→ no maturation of the

ovarian follicles.

During Lactation

High level of prolactin → inhibits ovarian response to FSH → no follicular growth → hypoestrogenic state → no menstruation. If the patient does not breastfeed her baby, the menstruation returns by 6th week following delivery in about 40 percent and by 12th week in 80 percent of cases. If the patient breastfeeds her baby, the menstruation may be suspended in about 70 percent until the baby stops breast-feeding.

Menopause

No more responsive follicles are available in the ovaries for the gonadotropins to act. As a result, there is cessation of estrogen production from the ovaries with elevation of pituitary gonadotropins.

Classification of primary amenorrhoea.

Secondary sexual characteristics normal:

Imperforate hymen

Transverse vaginal septum

Absent vagina and functioning uterus

Absent vagina and non-functioning uterus

XY female: androgen insensitivity

Resistant ovary syndrome

Constitutional delay

Secondary sexual characteristics absent:

Normal stature

Hypogonadotrophic hypogonadism

Congenital

Isolated gonodotrophin-releasing hormone deficiency

Olfactogenital syndrome

Acquired

Weight loss/anorexia

Excessive exercise

Hyperprolactinaemia

Hypergonadotrophic hypogonadism

Gonadal agenesis

XX agenesis

XX or XY agenesis

Gonadal dysgenesis

Turner mosaic

Other X deletions or mosaics

XY enzymatic failure

Ovarian failure

Galactosaemi

Short stature

Hypogonadotrophic hypogonadism

Congenital

Hydrocephalus

Acquired

Trauma

Empty sella syndrome

Tumours

Hypergonadotrophic hypogonadism

Turner syndrome

Other X deletions or mosaics

Heterosexual development

Congenital adrenal hyperplasia

Androgen-secreting tumour

5α-Reductase deficiency

Partial androgen receptor deficiency

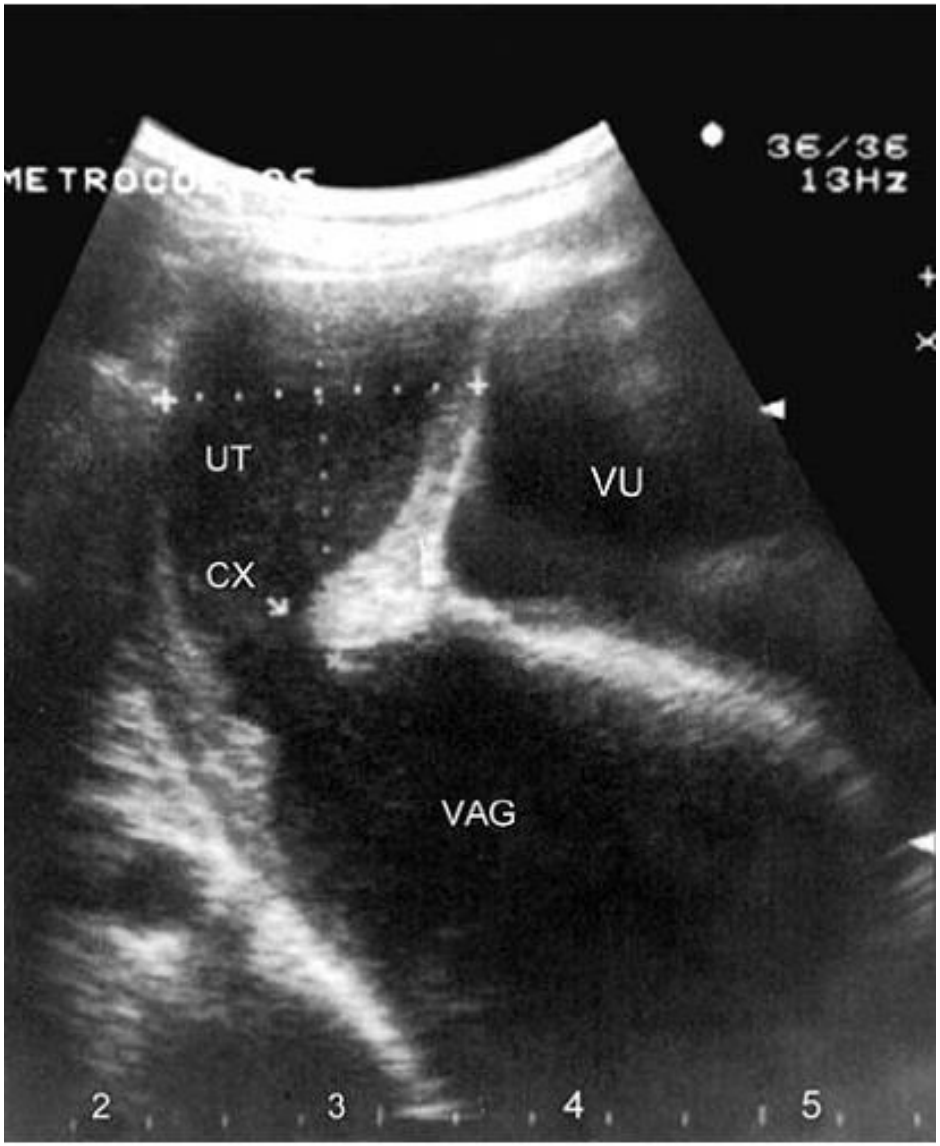
True hermaphrodite

Absent Müllerian inhibitory factor

Normal secondary sexual characteristics

Imperforate hymen

- The imperforate hymen may present at two stages of development. It may present in early childhood when the infant presents with a bulging hymen (mucocele).
- It may also present in later life when a pubertal girl complains of **intermittent abdominal pain, which is usually cyclical.**
- The pain is due to dysmenorrhea associated with the accumulation of menstrual blood within the vagina.
- large quantities of blood to collect in some cases are known as **haematocolpos.**


36/36
13Hz
UT
VU
CX
VAG
2
3
4
5

- As the vaginal mass enlarges there may be associated difficulty with micturition and defecation.

- Examination will occasionally reveal an abdominal swelling and observation of the introitus will display a tense bulging bluish membrane, which is the hymen.

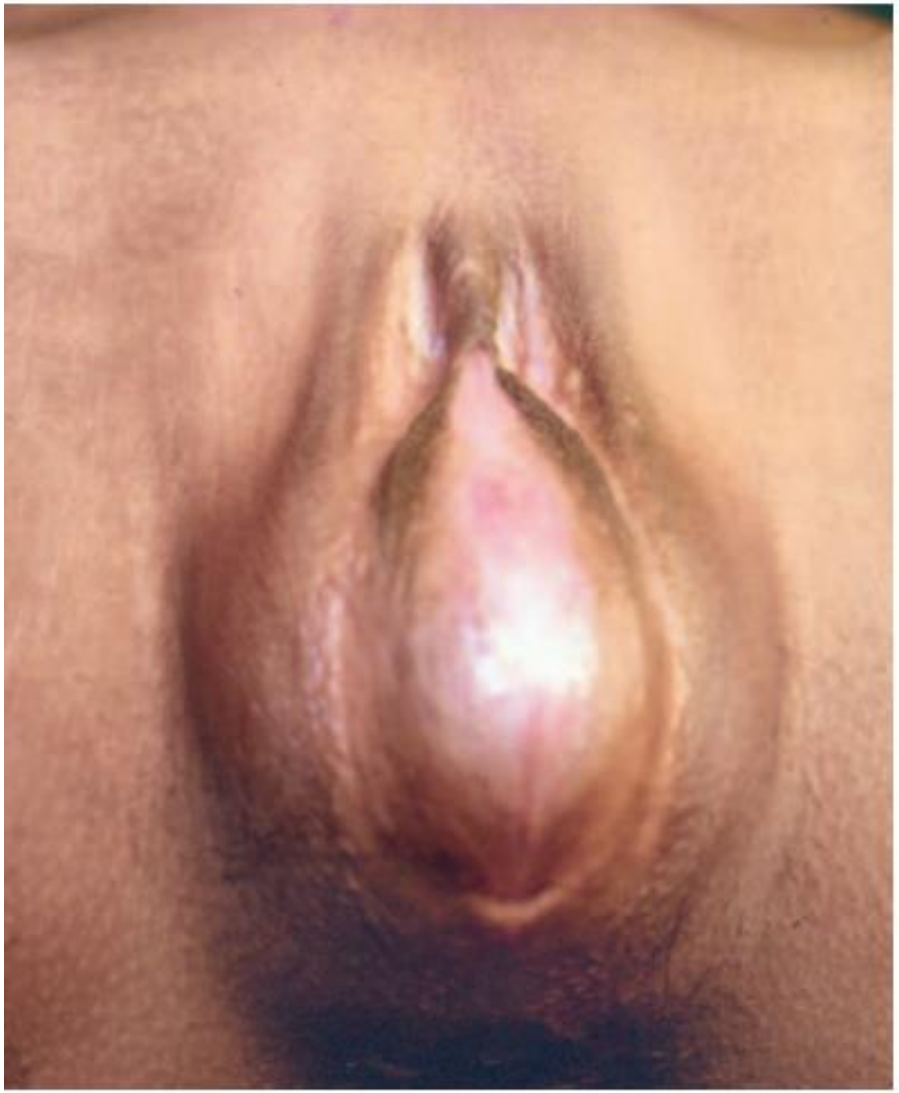


Fig. 4.3: Tense bulging of the hymen in hematocolpos

Absent vagina and a non-functioning uterus

- This is the second most common cause of primary amenorrhoea, second only to Turner's syndrome. Secondary sexual characteristics are normal as would
- be expected as ovarian function is unaffected .

Examination of the genital area shows normal female

- external genitalia but a blind-ending vaginal dimple This is known as Mayer–Rokitansky–Küster–Hauser (MRKH) syndrome and uterine development is usually absent.

It is important to remember that 40% of these patients have renal anomalies such as absent kidney, and there are also recognizable skeletal abnormalities associated with this syndrome.

XY female

There are a number of ways in which an individual may have an XY karyotype and a female phenotype,

and these include:

* Failure of testicular development.

* Enzymatic failure of the testis to produce androgen (particularly testosterone).

*** Androgenic receptor absence or failure of function.**

(androgen insensitivity syndrome)

This means that the masculinizing effect of testosterone during normal development is prevented and patients are therefore phenotypically female with normal breast development.

This occurs because of peripheral conversion of androgen to oestrogen and subsequent stimulation of breast growth.

Pubic hair is very scanty in these patients as there is no androgen response in target tissues.

The vulva is normal and the vagina is usually short.

The uterus and tubes are absent in this type of the XY female. The testes are usually found in the lower abdomen, but occasionally may be found in the hernial sacs in childhood, which alerts the surgeon to the diagnosis.

Presentation	Müllerian Agenesis	Androgen Insensitivity
Inheritance pattern	Sporadic	X-linked recessive
Karyotype	46,XX	46,XY
Breast development	Yes	Yes
Axillary and pubic hair	Yes	No
Uterus	No	No
Gonad	Ovary	Testis
Testosterone	Female levels	Male levels
Associated anomalies	Yes	No

Absent secondary sexual characteristics (normal height)

- Isolated GnRH deficiency (olfactogenital syndrome, Kallman's syndrome):

GnRH neurones are abscent due to partial or complete agenesis of olfactory bulb(olfactogenital dysgenesis). This disorder is charecterized by anosmia and colour blindness.

- Patients present with primary amenorrhea and menstruation can be induced by combined estrogen and progestin therapy. Induction of ovulation is

successful with exogenous gonadotropins.

Weight loss/anorexia

Weight loss is more commonly associated with secondary amenorrhea than primary amenorrhea,

but unfortunately it is increasingly apparent that young girls may suffer from anorexia nervosa in the prepubertal state.

This leads to failure of activation of the gene which initiates GnRH release in the hypothalamus, and

therefore a persistent hypogonadotrophic state exists. The growth spurt is not usually affected, but the

secondary sexual characteristics are absent.

Excessive exercise

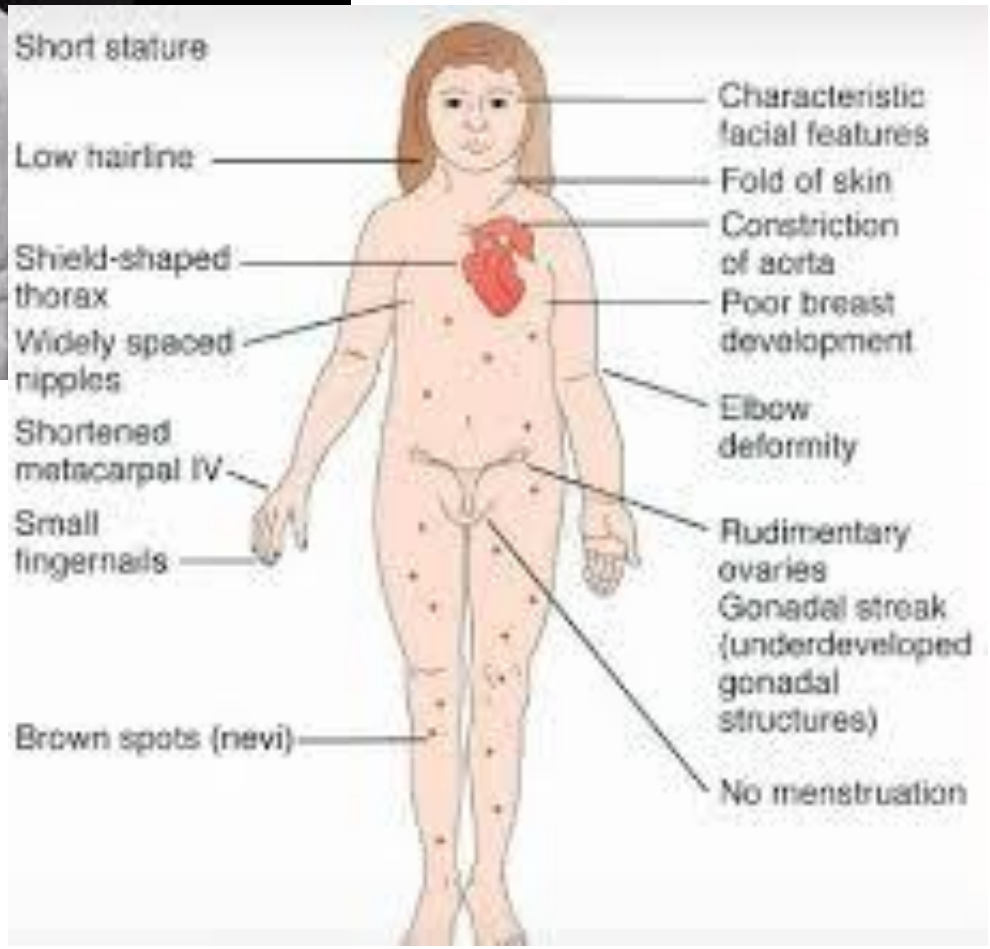
- Over recent years it has become increasingly recognized that excessive exercise in pubertal children leads to decreased body fat content, without necessarily affecting body mass.
- Development of muscle contributes to overall weight, and therefore weight alone cannot be used as the parameter for deciding whether there is an aetiology for their amenorrhea via this mechanism.
- A number of examples of this exist, including ballet dancers, athletes and gymnasts. These girls fail to menstruate and may actually develop frank anorexia nervosa.

Absent secondary sexual characteristics

(short stature)

Turner syndrome:

- In pure Turner's syndrome the chromosome complement is 45X0 and here a syndrome of short stature and ovarian failure lead to typical features.
- These children usually present in the teenage years, because of failure of development of secondary sexual characteristics or, more commonly, are referred from growth clinics for induction of induction of secondary sexual characteristics.


Short stature
Low hairline
Shield-shaped thorax
Widely spaced nipples
Shortened metacarpal IV
Small fingernails
Brown spots (nevi)
Characteristic facial features
Fold of skin
Constriction of aorta
Poor breast development
Elbow deformity
Rudimentary ovaries
Gonadal streak (underdeveloped gonadal structures)
No menstruation

Evaluation and management

constitutional delay is the most common diagnosis. This diagnosis of constitutional delay should only be made when all other syndromes have been excluded.

Normal secondary sexual characteristics

The presence of normal secondary sexual characteristics should alert the clinician to the presence of outflow tract obstruction. This is the most common cause of primary amenorrhea in the presence of normal secondary sexual characteristics.

It is simple to do a pelvic ultrasound scan to assess the

pelvic anatomy(rarely we need to do CT scan or MRI).

If the uterus is abscent, the karyotype should be performed; if this **is 46XX, then MRKH syndrome**

is the most likely diagnosis.

If the chromosome complement is 46XY, the patient is, by definition, an XY female.

Management:

1. If the uterus is present on ultrasound, then there may be an associated haematocolpos and hematometra and appropriate reconstructive surgery should be carried out.

- Patients with an absent uterus require special psychological counselling . At the appropriate time a vagina may be created either non-surgically or surgically. In 85% of cases the use of vaginal diltors is successful.
- In girls found to have an XY karyotype, careful counselling is necessary over the malignant potential of their gonads, this being reported in about 30% and it is important for them to have their gonads removed.
- All patients should be informed of their karyotype when appropriate.

2. In outflow tract obstruction, surgical management may occur at various levels.

- The simplest form is an imperforate hymen and in this condition a cruciate incision in the hymen allows drainage of the retained menstrual blood.
- Transverse vaginal septae are much more difficult to deal with and require specialist reconstruction to create a vagina which is subsequently functional.

3. If investigations suggest constitutional delay and development of secondary sexual characteristics is complete, there is no need to suggest any treatment other than annual review.

it may be useful to promote a menstruation using the oral contraceptive pill for one cycle to prove that menstruation can occur and this can be very reassuring.

Absence of secondary sexual characteristics

In this particular situation, it is extremely important to make an assessment of the patient's height.

1. If the patient of normal height for age, measurement gonadotrophins will reveal levels that are either low or high.

- Low levels of gonadotrophins confirm the diagnosis of hypogonadotrophic hypogonadism, while elevated levels should provoke the clinician to perform a karyotype. The 46XX patient will have premature ovarian failure, resistant ovary syndrome or gonadal Agenesis while the XY female will have 46xy gonadal agenesis or testicular enzymatic failure.

2. If stature is short, gonadotrophin levels will either be low (associated with an intracranial lesion) or high (which, following a karyotype) almost certainly Turner's syndrome

Management:

In patients with hypogonadotrophic hypogonadism, treatment should be to manage accordingly:

1.In isolated GnRH deficiency, hormone replacement therapy will need to be instituted to induce development of the secondary sexual characterisics. These patients are infertile and that ovulation induction in the future can be invoked using various fertility regimens.

- Hormone replacement therapy is essential and regimens exist for the induction of secondary sexual characteristics over 3–5 years.
- Oestrogen should be used alone for about 2 years, and then 2–3 years of gradual introduction of progestogens, thereby establishing normal breast growth over a time frame that is equivalent to normal.

Patients with an XY dysgenesis or enzymatic failure should have gonadectomies performed to avoid malignancy.

- It must always be remembered that any chronic medica illness which prevents normal growth will result in delayed onset of puberty and these causes must be considered in any patient presenting in this way.